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Autosomal Recessive Lateralization and Midline Defects: Blastogenesis Recessive 1

Sophie Debrus,[1] Ursula Sauer,[3] Simone Gilgenkrantz,[5] Wolfgang Jost,[4] Hans-Jürgen Jesberger,[4] Patrice Bouvagnet[1,2*]

[1]*CRBM, CNRS UPR 9008, Montpellier, France*
[2]*Service de Cardiologie B, Hôpital A. de Villeneuve, Montpellier, France*
[3]*Kinderklinik, Deutsches Herzzentrum München, München, Germany*
[4]*Universitätsklinik für Kinder- und Jugendmedizin, Neuropädiatrische Abteilung, Homburg/Saar, Germany*
[5]*Laboratoire de Génétique, Vandoeuvre les Nancy, France*

In this report, we present 2 sibships in which midline and lateralization anomalies are demonstrated. Because midline and lateralization processes are early embryological events, we suggest calling this sequence Blastogenesis Recessive 1 (BGR1). Since connexin 43 gene mutations were demonstrated in some polyasplenia patients and according to connexin 43 temporospatial tissue expression, we hypothesize that this gene could bear mutations responsible for the anomalies reported in these two sibships. Am. J. Med. Genet. 68:401–404, 1997.
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KEY WORDS: lateralization defect; midline; cardiac malformation; autosomal recessive; blastogenesis

INTRODUCTION

Recently it was demonstrated epidemiologically that "infants with midline anomalies have alterations of the normal body asymmetry more frequently than infants without midline defects" [Martínez-Frías et al., 1995]. This observation was suggested by Opitz on the hypothesis that such anomalies were the consequence of abnormal development during blastogenesis [Opitz, 1993]. During this stage, the embryo acquires craniocaudal, dorsoventral and left/right axes. A defect of midline formation may alter the lateralization process which may cause normally asymmetrical organs to become inverted or symmetrical, or normally symmetrical organs to become asymmetrically developed.

We report here two families in which affected members have midline and/or lateralization anomalies which seem to segregate as an autosomal recessive trait. We suggest calling this sequence Blastogenesis Recessive 1 (BGR1).

CLINICAL REPORTS

Family 1

Individual II-1. The oldest daughter (Fig. 1) has dextrocardia and atresia of the pulmonary trunk. She was operated on and is now doing well. The chromosome analysis was normal (46,XX).

Individual II-2. The younger daughter has complex anomalies. Pregnancy was complicated by bleeding during the first trimester. The alpha-fetoprotein level was above normal in the mother's blood and amniotic fluid. Ultrasound did not show NTD but an increased distance between the cerebral ventricles.

At birth, she had cleft of the soft palate with bifid uvula, microcephaly (head circumference 31.5 cm) with a short forehead. She also had asymmetrical buttocks folds although a dislocation hip was eliminated by clinical examination. Later, she had numerous urographies which showed normal and symmetrical hips.

On the computer tomography and ultrasound examination of the brain, she demonstrated a left anterior horn rudimentary, hypoplasia of the corpus callosum and dysgenesis of the lower parts of the cerebellum. Two large cyst formations were also seen: one along the median line on the left side and one in the temporal lobe (Fig. 2). In addition, she had bilateral coloboma of the papilla of the optic nerve, chorioretinal atrophy with no distinguishable macula, and on the left eye a retinal temporal fold. Because of recurrent urinary infections, she had an urography which disclosed two kidneys and ureters on the left side both connecting to the vagina. The right urinary tract was normal. She also has an anomaly of the external genitalia with a small opening to the vagina next to the urethral meatus. She has severe vertebral defects including several hemivertebrae and increase in the interpedicular distance

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*Correspondence to: Patrice Bouvagnet, M.D., Ph.D., CRBM, CNRS-INSERM, 1919 route de Mende, 34033 Montpellier, France.

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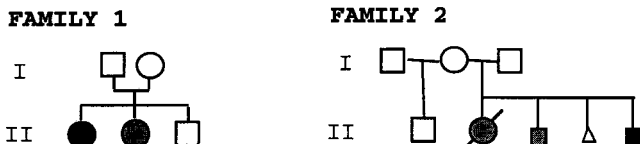

Fig. 1. Presentation of pedigrees. Filled symbols represent females (circles) or males (squares) with lateralization defects. Shaded symbols are individuals with midline or cardiac defects. Crossed symbols represent deceased persons. Abortions are represented by small symbols (a circle, square, or triangle for a female, male, or sex unknown fetus, respectively).

in the lumbar spine (Fig. 3). No lateralization defect per se was demonstrated in a sense that she has no left/right inversion of sidedness. At the age of 8 months, she developed seizures and psychomotor retardation was evident. At age 5 years, a benign nephrogenic adenoma of the ostium of the left ureter was excised.

Parents have no lateralization anomaly (chest roentgenogram and abdominal ultrasound normal). The brother (II-3) is normal and the family history is otherwise unremarkable. Chromosomes of the two sisters and her parents were normal.

Family 2

This woman had a normal child from her first union but had a child with a major malformation and 2 terminated pregnancies for fetal malformations from her second union (Fig. 1).

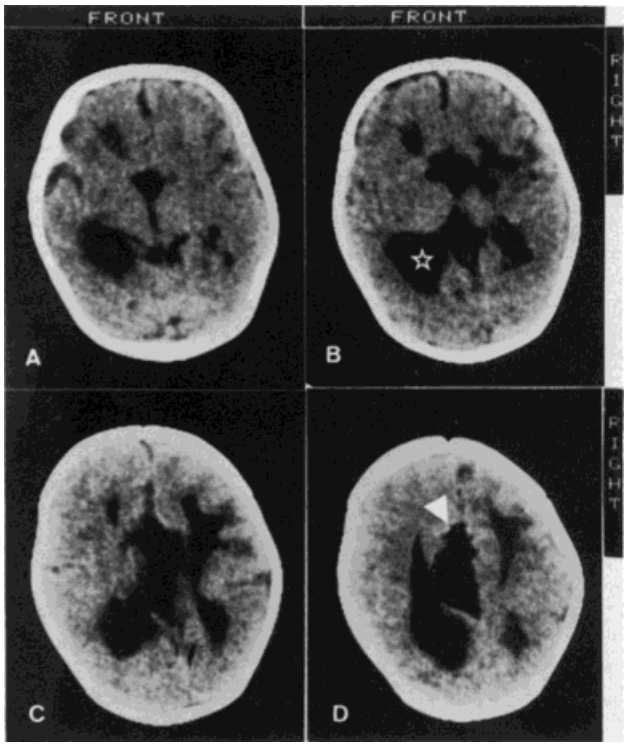

Fig. 2. Computer tomography scan of patient II-2 of family 1 at the age of three months. From **A** to **D**, transversal sections towards the top of the head. The white star indicates the temporal cyst. The white arrow-head points to the paramedian cyst which extends to the top of the head.

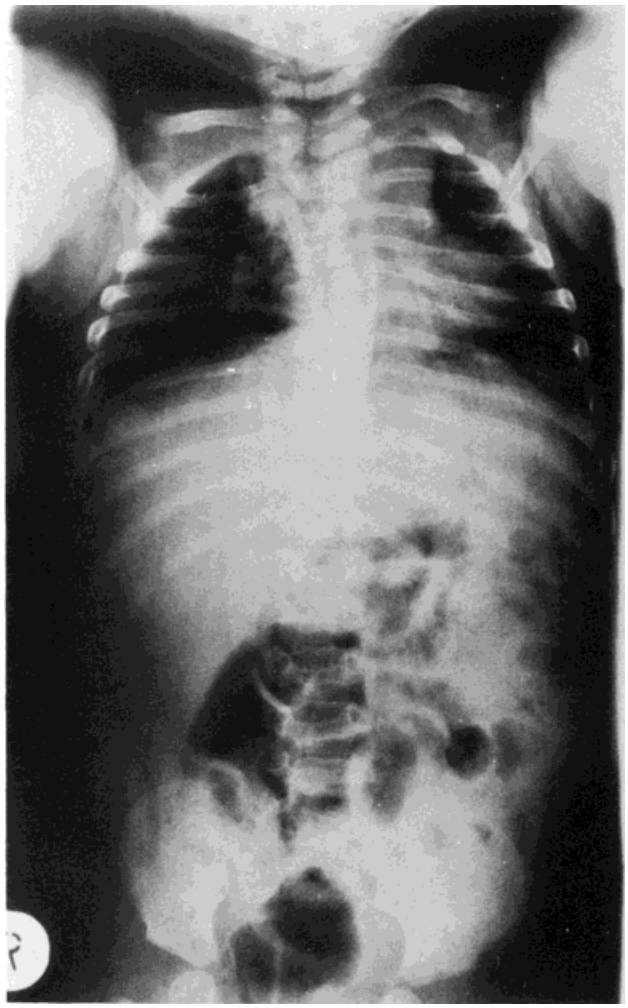

Fig. 3. Roentgenogram of patient II-2 of family 1 at the age of 5 months old. She has severe spinal dysplasia with sagittal cleft vertebrae, a vertebral bar on the right side and a first right rib hypoplastic or absent.

Individual II-2. Died at age 19 days. She had a complete atrioventricular canal with hypoplastic mitral valve and left ventricle. The blood flow from the ventricles to the aorta was restricted by a severe subaortic stenosis. No other malformations were present.

Individual II-3. Ultrasound examination at 15 weeks of gestation showed a complete isolated rachischisis. No other malformations were evidenced. Chromosomes were normal (46,XY).

Individual II-5. Gestation was medically terminated at 19 weeks of gestation because ultrasound monitoring evidenced complex cardiac malformations with heterotaxy and moderate hypoplasia of the vermis. At autopsy, the male fetus had two left-type lungs, an enlarged heart with a common atrium draining pulmonary veins and a right superior vena cava. He had left superior vena cava to the coronary sinus, hypoplastic right ventricle, subaortic ventricular septal defect, hypoplastic pulmonary artery, and right aortic arch. The stomach was on the right side with scattered mi-

crosplenia. The biliary duct was strictly median. Histological examination of liver, kidneys, pancreas, adrenal glands, and lungs were normal.

The two parents were normal (chest roentgenogram) and had normal karyotypes. The family history on both parental sides was unremarkable.

DISCUSSION

One individual in family 1 and two individuals in family 2 have midline defects (cleft of soft palate, bifid uvula, corpus callosum dysgenesis, hypoplastic vermis, and rachischisis). In addition, lateralization anomalies were noted and can be sorted into two groups: 1) disturbance of normal asymmetry which is replaced by abnormal symmetry (left or right sidedness: two left type lungs, persistence of the left superior vena cava) and 2) inversion of sidedness (dextrocardia, abdominal situs inversus, right aortic arch). By contrast, asymmetrical buttocks fold, left anterior horn rudimentary, two left kidneys and ureters, hemivertebrae may not be defects of lateralization (perturbation of normal symmetry) but rather of blastogenesis.

Because lateralization defects may be associated with additional anomalies whatever the mode of transmission, we thought that it would be interesting to compare these manifestations which are not simple inversion of sidedness or part of heterotaxy such as asplenia/polysplenia. Table I presents these data. There are clear overlaps between these 3 sequences which suggest that the molecular defects act on a common pathway and probably at the same stage in the 3 sequences. Moreover, in some instances, it might be difficult to distinguish autosomal dominant from X-linked inheritance because female carriers are affected [Mikkilä et al., 1994].

A report recently demonstrated mutations in the connexin 43 gene in 6 patients with polyasplenia [Britz-Cunningham et al., 1995]. Connexins are a multigene family which encodes for protein of gap junction [Willecke et al., 1990]. Gap junctions are specialized regions of adjoining cell membranes composed of numerous intercellular channels. These channels allow passive diffusion of ions and small molecules (up to 1 kDa) and are thought to play a role in excitable tissue by conducting electric signals between cells but also in non-excitable tissue in cell growth and differentiation. Moreover, connexin 43 is expressed in the early stages of mouse development at a time when groups of cells are known to form developmental compartments [Lo and Gilula, 1979].

It seems that gap junctions, by defining communication compartments, are directly involved in the process of pattern formation. Moreover, connexin 43 is expressed in the mouse embryo during gastrulation in the ectoderm layer from which the tissues of the fetus originate [Yancey et al., 1992]. As a consequence, one might expect, that a "hit" on one of the embryonic cells has a consequence on the whole embryo. This is precisely the hypothesis of Opitz who considers the embryo as a "primary field" at this stage [Opitz, 1993].

At this point, it is not clear whether all lateralization defects have a mutation in the connexin 43 gene but

TABLE I. Defects Associated With Autosomal Recessive, Dominant, and X-Linked Heterotaxy*

Type of defects	Autosomal recessive	Autosomal dominant	X-linked
Buccal	Bifid uvula Cleft palate	Cleft palate	
Skeletal	Hemivertebrae Sagittal cleft vertebrae Interpediculate distance	Spondylolysis Hypertelorism	Scoliosis, pectus excavatum Hypertelorism Coccygeal, sacral dysgenesis Dislocated hips, club foot Absence of left thumb
Neural	Rachischisis, Corpus callosum dysgenesis Coloboma Epilepsy	Anencephaly Corpus callosum dysgenesis Enlarged posterior fossa	Meningomyelocele Arhinencephaly Cerebellar hypoplasia
Heart	AVC Hypoplasia of PA Hypoplastic left heart	AVC Aortic atresia Tetralogy of Fallot Single ventricle Right aortic arch	AVC TGA Tetralogy of Fallot Single ventricle Right aortic arch
Urinary	2 kidneys and ureters on one side	Crossed fused renal ectopia Horseshoe kidney Urinary retention/reflux	Agenesis of both kidneys 2 kidneys or ureters on one side Urinary retention Rectovesical fistula
Genital	Opening to the vagina Ureter to the vagina		No scrotum Septate vagina and uterus
Tumor	Ureteral adenoma	Choroidal nevus	Coccygeal fibrolipoma

*AVC, atrioventricular canal; PA, pulmonary artery; TGA, transposition of the great vessels.
Only the most frequent cardiac malformations are presented. Autosomal recessive anomalies are from this article, autosomal dominant are from de Meeus et al. [1997], and X-linked anomalies are from Mathias et al. [1987] and Mikkilä et al. [1994].

we hypothesize that sequences of lateralization and midline anomalies, as in this report, may also have a mutation in the connexin 43 gene. This gene is not only expressed during blastogenesis but also during organogenesis, particularly in the forming eye, which might explain the coloboma of one of the reported patients. Because of the concomitant occurrence of midline and lateralization anomalies in these sibships, we suggest calling this sequence Blastogenesis Recessive 1.

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